Chromosome segregation model - detailed description

March 28, 2012

Introduction

This is a more detailed version of the kinetochore segregation model to be published in the JCB article, which should be referred to for all the experimental, biological and non-technical aspects of this work.

1 Definitions

1.1 State vector

The mitotic spindle is described by the speeds and position along the x axis of two spindle pole bodies, N chromosomes with two centromeres and M_k attachment sites per centromere.

Positions are noted as follow:

- The left and right spindle pole bodies (SPBs), x_s^L and x_s^R
- The N centromeres, x_n^A, $x_n^B, n \in \{1, \cdots, N\}$
- The M_k attachment sites of each centromere, x_{nm}^A, $x_{nm}^B, n \in \{1, \cdots, N\}, m \in \{1, \cdots, M_k\}$

The speeds are noted with a dot: $dx/dt = \dot{x}$.

As all the interactions are assumed to be parallel to the spindle axis, only the positions along this axis are considered, in a coordinate system with its origin at the center of the spindle, which means that $x_s^L(t) = -x_s^R(t) \, \forall t$.

1.2 Random variables for the attachment

We define ρ_{nm}^A and λ_{nm}^A, two random variables that govern the attachment state of the site x_{nm}^A, such that:

$$\rho_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the right SPB} \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

$$\lambda_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the left SPB} \\ 0 & \text{otherwise} \end{cases} \tag{2}$$

Note that ρ_{nm}^A and λ_{nm}^A are not independent, as an attachment site can't be attached to both poles. To take this into account, we can define the variable $\pi_{nm}^A = \rho_{nm}^A - \lambda_{nm}^A$ such that:

$$\pi_{nm}^A = \begin{cases} -1 & \text{if the site is attached to the left SPB} \\ 0 & \text{if the site is not attached} \\ 1 & \text{if the site is attached to the right SPB} \end{cases} \tag{3}$$

We have:

$$\lambda_{nm}^{A} = \pi_{nm}^{A}\left(\pi_{nm}^{A} - 1\right)/2 \tag{4}$$
$$\rho_{nm}^{A} = \pi_{nm}^{A}\left(\pi_{nm}^{A} + 1\right)/2 \tag{5}$$

We also define N_n^{AL} and N_n^{AR} as the number of ktMTs of centromere A attached to the left and right SPBs, respectively:

$$N_n^{AL} = \sum_{m=1}^{M_k} \lambda_{nm}^{A} \text{ and } N_n^{AR} = \sum_{m=1}^{M_k} \rho_{nm}^{A} \tag{6}$$

Note that $N_n^{AL} + N_n^{AR} \leqslant M_k \,\forall\, \pi_{nm}$ The same definitions apply for the centromere B and left SPB.

1.3 Forces

The following force balances are considered:

1.3.1 Forces at the right SPB :

- Friction forces (viscous drag): $F_f^R = -\mu_s \dot{x_s}^R$
- Midzone force generators:

$$F_{mid} = F_z\left(1 - (\dot{x}_s^R - \dot{x}_s^L)/V_z\right) = F_z\left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$F_{kMT}^{T} = \sum_{n=1}^{N}\sum_{m=1}^{M_k} - \rho_{nm}^{A} F_k\left(1 - (\dot{x}_{nm}^{A} - \dot{x}_s^R)/V_k\right) - \rho_{nm}^{B} F_k\left(1 - (\dot{x}_{nm}^{B} - \dot{x}_s^R)/V_k\right)$$

1.3.2 Forces at the left SPB :

Because of the reference frame definition, $\dot{x_s}^R = -\dot{x_s}^L \,\forall t$. Here we substituted x_s^L with $-x_s^R$

- Friction forces (viscous drag): $F_f^L = \mu_s \dot{x_s}^R$
- Midzone force generators:

$$F_{mid}^{L} = -F_z\left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$F_{kMT}^{T} = \sum_{n=1}^{N}\sum_{m=1}^{M_k} - \lambda_{nm}^{A} F_k\left(1 + (\dot{x}_{nm}^{A} + \dot{x}_s^R)/V_k\right) - \lambda_{nm}^{B} F_k\left(1 + (\dot{x}_{nm}^{B} + \dot{x}_s^R)/V_k\right)$$

1.3.3 Forces at centromere An

- Drag: $F_c^f = -\mu_c \dot{x_n}^A$
- Cohesin bond (Hook spring) restoring force exerted by centromere[1]:

$$F_{BA} = \begin{cases} \kappa_c(x_n^B - x_n^A - d_0) & \text{if} \quad d_0 < x_n^A - x_n^B \\ 0 & \text{if} \quad -d_0 < x_n^A - x_n^B < d_0 \\ \kappa_c(x_n^B - x_n^A + d_0) & \text{if} \quad x_n^A - x_n^B \end{cases} \tag{7}$$

  With $F_{AB} = -F_{BA}$.

- Total visco-elastic bond between the centromere A and the attachment sites:

$$F_v^T = \sum_{m=1}^{M_k} -\kappa_k(x_n^A - x_{nm}^A) - \mu_k(\dot{x}_n^A - \dot{x}_{nm}^A)$$

1.3.4 Forces at attachment site Anm

- Visco-elastic bond between the centromere A and the attachment sites:

$$F_v = \kappa_k(x_n^A - x_{nm}^A) + \mu_k(\dot{x}_n^A - \dot{x}_{nm}^A)$$

- Kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^A =& \rho_{nm}^A F_k \left(1 - (\dot{x}_{nm}^A - \dot{x}_s^R)/V_k\right) - \lambda_{nm}^A F_k \left(1 + (\dot{x}_{nm}^A - \dot{x}_s^L)/V_k\right) \\ =& \rho_{nm}^A F_k \left(1 + (\dot{x}_s^R - \dot{x}_{nm}^A)/V_k\right) - \lambda_{nm}^A F_k \left(1 + (\dot{x}_{nm}^A + \dot{x}_s^R)/V_k\right) \end{aligned} \tag{8}$$

For now on, we are taking F_k as unit force and V_k as unit speed and substituting λ_{nm}^A and ρ_{nm}^A with π_{nm}^A:

$$F_{kMT}^A = -|\pi_{nm}^A|\dot{x}_{nm}^A + \pi_{nm}^A(1 + \dot{x}_s^R) \tag{9}$$

1.4 Set of first order coupled equations

In the viscous nucleoplasm, inertia is negligible. Newton first principle thus reduces to: $\sum F = 0$. This force balance equation can be written for each elements of the spindle. To simplify further, the equations for the right and left SPBs can be combined. With the same substitutions as before:

$$-2\mu_s\dot{x}_s^R + 2F_z\left(1 - 2\dot{x}_s^R/V_z\right) + \sum_{n,m} |\pi_{nm}^A|\dot{x}_{nm}^A + |\pi_{nm}^B|\dot{x}_{nm}^B - \left(\pi_{nm}^A + \pi_{nm}^B\right)\left(1 + \dot{x}_s^R\right) = 0 \tag{10}$$

All the equations are gathered together in the system of equations:

$$\mathbf{A}\dot{X} + \mathbf{B}X + C = 0$$

The vector X has $1 + 2N(M_k + 1)$ elements and is defined as follow[2]:

$$X = \{x_s^R, \{x_n^A, \{x_{nm}^A\}, x_n^B, \{x_{nm}^B\}\}\} \text{ with } n \in 1 \cdots N \text{ and } m \in 1 \cdots M_k$$

[1] We want the centromeres to be able to cross each over. In one dimension, this introduces a discontinuity. In the previous version, the 'swap' mechanism was solving this directly (as x_A and x_B are exchanged). This is not possible any more, as the 'swap' mechanism is now irrelevant, as there is no prefered side for a given centromere. With this model, the discontinuity is only to the first order. I am convinced there can be a better regularisation.

[2] Note that the left SPB is omitted in X.

In matrix form, we have:

$$
X = \begin{pmatrix} x_s^R \\ x_n^A \\ x_{nm}^A \\ x_n^B \\ x_{nm}^B \end{pmatrix}
$$

$$
A = \begin{pmatrix} -2\mu_s - 4F_z/V_z - \sum(\pi_{nm}^A + \pi_{nm}^B) & \dots & \pi_{nm}^A & \dots & \pi_{nm}^B \\ \dots & -\mu_c - M_k\mu_k & \mu_k & \dots & \\ \pi_{nm}^A & \mu_k & -\mu_k + |\pi_{nm}^A| & \dots & \\ \dots & & & -\mu_c - M_k\mu_k & \mu_k \\ \pi_{nm}^B & \dots & & \mu_k & -\mu_k + |\pi_{nm}^B| \end{pmatrix},
$$

$$
B = \begin{pmatrix} 0 & \dots & & & \\ \dots & -|\delta_n^{AB}|\kappa_c - M_k\kappa_k & \kappa_k & |\delta_n^{AB}|\kappa_c & \dots \\ \dots & \kappa_k & -\kappa_k & \dots & \\ \dots & |\delta_n^{AB}|\kappa_c & \dots & -|\delta_n^{AB}|\kappa_c - M_k\kappa_k & \kappa_k \\ \dots & & \kappa_k & & -\kappa_k \end{pmatrix}
$$

$$
C = \begin{pmatrix} 2Fz - \sum_{n,m}(\pi_{nm}^A + \pi_{nm}^B) \\ \delta_n^{AB}\kappa_c d_0 \\ \pi_{nm}^A \\ -\delta_n^{AB}\kappa_c d_0 \\ \pi_{nm}^B \end{pmatrix} \text{ with } \delta_n^{AB} = \begin{cases} 1 & \text{if} \quad d_0 < x_n^A - x_n^B \\ 0 & \text{if} \quad -d_0 < x_n^A - x_n^B < d_0 \\ -1 & \text{if} \quad x_n^A - x_n^B \end{cases} \tag{11}
$$

As is actually done in the python implementation, A can be decomposed into a time invariant part A_0 and a variable part A_t with:

$$
\begin{aligned}
A_0 &= \begin{pmatrix} -2\mu_s - 4F_z/V_z & \dots & & & \\ \dots & -\mu_c - M_k\mu_k & \mu_k & \dots & \\ \dots & \mu_k & -\mu_k & \dots & \\ \dots & & & -\mu_c - M_k\mu_k & \mu_k \\ \dots & & & \mu_k & -\mu_k \end{pmatrix} \\
A_t &= \begin{pmatrix} -\sum(\pi_{nm}^A + \pi_{nm}^B) & \dots & \pi_{nm}^A & \dots & \pi_{nm}^B \\ \dots & & & & \\ \pi_{nm}^A & \dots & |\pi_{nm}^A| & \dots & \\ \dots & & & & \\ \pi_{nm}^B & \dots & & & |\pi_{nm}^B| \end{pmatrix}
\end{aligned} \tag{12}
$$

Equivalently for B:

$$
B_0 = \begin{pmatrix} 0 & \dots & & \\ \dots & -M_k\kappa_k & \kappa_k & \dots \\ \dots & \kappa_k & -\kappa_k & \dots \\ \dots & \dots & -M_k\kappa_k & \kappa_k \\ \dots & & \kappa_k & -\kappa_k \end{pmatrix} = \kappa_k \begin{pmatrix} 0 & \dots & & \\ \dots & -M_k & 1 & \dots \\ \dots & 1 & -1 & \dots \\ \dots & \dots & -M_k & 1 \\ \dots & & 1 & -1 \end{pmatrix} \tag{13}
$$

And

$$
B_t = \kappa_c \begin{pmatrix} 0 & \dots & & & \\ \dots & -|\delta_n^{AB}| & \dots & |\delta_n^{AB}| & \dots \\ \dots & & & & \\ \dots & |\delta_n^{AB}| & \dots & -|\delta_n^{AB}| & \dots \\ \dots & & & & \end{pmatrix} \tag{14}
$$